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Editorial Comment

Progressive Inadequacy of Vascular Support in Myocardial Hypertrophy*

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Hypertrophy: advantages and eventual disadvantages. Unlike other organs subject to hemodynamic overload, the myocardium responds by hypertrophy; survival compels coronary vascular adaptation. Left ventricular hypertrophy, the common structural response to a variety of overloads, can be compensatory early but detrimental when it progresses without effective treatment. Left ventricular hypertrophy initially decreases wall stress but ultimately induces contraction and relaxation abnormalities and vulnerability to arrhythmias, particularly if it is associated with coronary disease. Moreover, although left ventricular hypertrophy may limit infarct expansion (1), infarcts are larger in hypertrophic ventricles (2), perhaps because of inadequate growth factors for angiogenesis of collateral channels (3). Even with normal epicardial arteries, the vascular hierarchy from capillaries through arterioles and intramural arteries responds in proportion to the severity and duration of hypertrophy and its pathogenetic process. Consequently, left ventricular hypertrophy that exceeds its vascular support at any level becomes ischemic; moreover, left ventricular hypertrophy disproportionate to diastolic volume permits wall stress to increase unchecked and, with it, oxygen demand, independent of vascular conditions.

Myocardial/microvascular flow disproportion. Myocardial and vascular growth need not proceed in parallel. Although myocardial fibers hypertrophy as a cube function and capillary surface increases only as a square function, early left ventricular hypertrophy may be adequate for demands during rest. Yet increased total coronary dimensions and flow, initially compensatory, are ultimately outpaced by increasing ventricular mass, reducing flow per unit of myocardium (4,5). In the microvasculature, capillary diameters may be similar in normal and hypertrophic ventricles, but *total capillary surface decreases in left ventricular hypertrophy* and, despite normal arteriolar density (6), greater intercapillary separation (7) increases distances for blood-myocardial exchange of nutrients and metabolites. Extravascular compression by hypertrophic muscle and decreased capacity for maximal vasodilation exacerbate these disadvantages. The resultant *decreased coronary reserve* is minimal in early left ventricular hypertrophy and is often evident only as a response to physiologic or paced tachycardia or to hypoxic or induced (e.g., adenosine) vasodilator stimuli, or as abnormal reactive hyperemia; it worsens disproportionately with progressive left ventricular hypertrophy. Decreased production of endothelium-derived relaxing factor may contribute (8) as may inappropriate vasoconstriction of prearteriolar vessels (9); both exacerbate the increased arteriolar wall to lumen ratio in left ventricular hypertrophy (10) with abnormal shear stress at the blood-endothelial interface (11). Even in "pure" left ventricular hypertrophy, increased left ventricular mass alone greatly increases coronary resistance and decreases flow reserve (maximal/rest flow ratio). Coronary venous compression probably adds to total coronary resistance.

Any increased cavity pressure will also compress subendocardial vessels, whereas abnormal myocardial relaxation additionally tends to compress intramural coronary vessels, further shifting transmural blood flow (12,13). Because 80% of left ventricular coronary flow is diastolic, prolonged systole, due mainly to prolonged left ventricular ejection time in compensated aortic stenosis (14), prolongs "physiologic" systolic ischemia and encroaches on diastolic time for flow and metabolic recuperation (for example, time for cytosolic calcium ion to return to the sarcoplasmic reticulum). Thus, the normally relatively ischemic subendocardial circulation is further hypoperfused in left ventricular hypertrophy during exercise, tachycardia and vasodilator stimulation, with a more unfavorable shift toward the mid- and subepicardial layers (15) contributing to any clinical ischemia.

Vasculature in aortic stenosis. In aortic stenosis normal coronary conduit arteries may permit appropriate left ventricular hypertrophy with normal cavity size and better function (16). Yet minor increases in epicardial coronary resistance affect total coronary resistance very little compared with the great *selective decrease of microvascular reserve* in severe aortic stenosis with left ventricular hypertrophy. The latter, a mechanism for angina with unobstructed epicardial coronary arteries, can be conceived as a special case of "syndrome X." Thus, major coronary narrowing could be disastrous because low poststenotic coronary pressure exacerbates the downstream flow-limiting effects of extravascular compression (17) and the other determinants of decreased coronary reserve, whereas enlargement of conduit arteries, even proportional to myocardial hypertrophy, would have little effect on microvascular ischemia.

Vasculature in volume and pressure overloading: present study. Volume and pressure loading by either aortic regurgitation or stenosis yield grossly similar directional effects on

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coronary reserve (18); systemic hypertension also does so (19) despite inclusion of the coronary orifices that are outside the overload zone of aortic valve disease. Intuitively, however, left ventricular hypertrophy differing in pathogenesis should have different associated effects at some levels. For example, patients with normal epicardial coronary arteries have much more angina with aortic stenosis than with aortic or mitral regurgitation and their respective coronary reserves differ correspondingly (20). Because the reduction in coronary reserve associated with left ventricular hypertrophy tends to be greater in humans than in experimental animals (21), the report by Villari et al. (22) in this issue of the Journal has dual importance as it involves both human subjects and progressive levels of left ventricular hypertrophy. The authors (22) might have reported on patients with aortic stenosis and regurgitation differentially, but they did not investigate the microvasculature. Nevertheless, their subjects, all with unobstructed epicardial coronary arteries, were selected because, with the exception of increased left anterior descending and left circumflex artery cross-sectional area, they were comparable at baseline to control subjects who underwent cardiac catheterization for chest pain. This increased cross-sectional area, when normalized for left ventricular mass, was initially comparable to that of control subjects, but it decreased significantly, becoming disproportionate as the patients' condition progressed from initially moderate to subsequent marked left ventricular hypertrophy.

In conclusion, progressively inadequate myocardial microvascular support converts progressive left ventricular hypertrophy from a transiently beneficial adaptation to an ultimately detrimental process. That the macrovascular circulation also fails to keep pace with myocardial growth requires further investigation.

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